REMARKS

I. Status of the Claims

Claims 1-35 were originally filed. Subsequently, claims 5 and 8-17 were canceled. Claims 1-4, 6, 7, 18, and 19 remain pending under examination.

II. Drawings

In the final Office Action mailed May 4, 2005, as well as in the previous Office Action, the drawings of this application were objected to for containing nucleic acid or amino acid sequences only, which the Examiner believed to be repetitive to the formal sequence listing and thus requested the amendment of the drawings. Applicants acknowledge the Examiner's concerns but respectfully request that the formal drawings submitted on December 18, 2003, be accepted in this application, because no specific provisions of the 37 C.F.R. or the MPEP require the removal of drawings containing only polynucleotide or amino acid sequences.

III. Claim Rejections

A. 35 U.S.C. §101

Claims 1-9, 18, and 19 were rejected under 35 U.S.C. §101 for alleged lack of either a specific, substantial, and credible asserted utility or a well established utility. Applicants respectfully traverse the rejection, particularly in light of the declaration under 37 C.F.R. §1.132 by Dr. Ken McCormack.

For reasons stated in the response filed on February 1, 2005, Applicants contend that the specification has asserted a specific and substantial utility for the claimed invention. This asserted utility is credible to a person of skill in the art, as established by Dr. McCormack's declaration filed herewith.

Dr. McCormack's Declaration

By way of Dr. McCormack's declaration, Applicants establish that the identification of human CNG3B, a novel beta subunit of a cyclic nucleotide gated cation channel,

does have a specific and substantial utility that is credible to one of skill in the art. Dr. McCormack states, in paragraph 6 of the declaration, that CNG3B forms, with other subunit(s), a cyclic nucleotide gated cation channel highly expressed in retina and testis. Upon direct binding of cyclic nucleotides such as cAMP and cGMP, the CNG3B cation channels are activated and become highly permeable to cations such as Na^+ and Ca^{2+}. This activation leads to cell membrane depolarization and increase of Ca^{2+} concentration within the cell. Since the CNG3B channels are capable of modulating cell membrane potential and cytoplasmic Ca^{2+} concentration, which, as a second messenger, participates in the regulation of signal transduction in relevant tissues, one of skill in the art would reasonably believe that the CNG3B channels are involved in modulating cellular excitability and therefore biological functions in these tissues. Because of the tissue-specific expression of CNG3B in retina and testes, an artisan would also reasonably believe that these CNG3B channels can serve as therapeutic targets for treatment of conditions related to aberrant cell excitability in the retina or testes, *e.g.*, visual disorders or male fertility disorders. The identification of human CNG3B gene therefore has a substantial utility, or a "real world" use, since this discovery makes possible the routine identification of activators and inhibitors of the CNG3B channels, which may be used as therapeutic agents for treating conditions caused by or related to abnormalities in vision or male fertility. This utility relies on the expression of CNG3B channels in the retina or testes and their involvement in the regulation of signal transduction in these tissues. These are specific features of the CNG3B cation channels and not a broad class of ion channels. Dr. McCormack thus concludes that the present invention has a specific utility.

Dr. McCormack goes on to explain that because the present invention not only provides nucleic acids encoding human CNG3B, but also teaches methods for detecting the activity of the CNG3B channels (*see, e.g.*, page 42, line 23, to page 46, line 2, of the specification) and methods for identifying modulators of the ion channels (*see, e.g.*, page 46, line 5, to page 50, line 19), upon reading this disclosure, a skilled artisan would be able to readily screen candidate compounds and identify activators or inhibitors of a CNG3B channel, without

the need to carry out extensive additional research. Dr. McCormack thus concludes that the present invention has a real-world use. See paragraph 7 of the declaration.

Concerning the therapeutic use of CNG3B modulators, Dr. McCormack explains that a CNG3B channel can serve as a therapeutic target for treating a condition, regardless of whether the CNG3B channel directly causes the condition. There are known instances where modulation of an ion channel is useful for treating a specific disease even though the ion channel itself may not directly cause the disease. For example, hypertension can be caused by a variety of illnesses such as renal disease and diabetes. Among the treatment strategies for hypertension is the use of drugs such as calcium channel blockers to relax the vasculature. Relaxing the vasculature to reduce blood pressure is useful and effective, even if the original cause of the hypertension is not directly related to vascular tone. Similarly, it is perfectly reasonable to expect that the targeting of a CNG3B channel, a cyclic nucleotide gated cation channel that is highly expressed in the retina and testes and is believed to play a role in regulating the biological functions of these tissues, is an appropriate strategy for treating vision disorders or male fertility disorders, whether or not such abnormality is directly caused by altered CNG3B channel activity. In other words, the use of CNG3B as a therapeutic target for treating these disorders is an effective approach whether or not other ion channels may be relevant to the disorders. Thus, Dr. McCormack concludes that the asserted utility of the CNG3B potassium channel of the present application is reasonable and therefore credible to an ordinarily skilled artisan. See paragraph 8 of the declaration.

It is therefore established that one of skill in the art, at the time the application was filed, would believe the physiological role human CNG3B plays in visual disturbances and male fertility, and would recognize the specific and real-world utility of the CNG3B encoding nucleic acids of the present invention.

Examiner's Specific Arguments

In the Final Office Action mailed May 4, 2005, the Examiner contended that Applicants' arguments were not convincing because (1) the assays for screening for modulators

of the CNG3B channels are not specific for this particular subunit; (2) the specification does not teach any such modulator, or whether inhibition or activation of the claimed CNG3B subunit is required for treating vision problems or male infertility; and (3) the specification does not teach any specific disease associated with the claimed CNG3B subunit (see page 5, lines 12-19, of the Final Office Action).

Applicants do not believe that these reasons are valid, nor are they relevant to the question of utility of this invention. First, the assays used for screening modulators of a CNG3B channel are indeed specific for this small class of ion channels—because the assays are carried out using a CNG3B channel, not just any ion channel, to demonstrate the possible effect on the activity of this ion channel by a candidate modulator. Second, since the pending claims are not directed to the modulators, there is no requirement to name the modulators. As Dr. McCormack has indicated in his declaration, the screening assays for CNG3B channel modulators are recognized by those of skill in the art as an effective means to allow identification of the modulators. Not naming the specific modulators is no reason to doubt the asserted utility of this invention. As far as the therapeutic use of a modulator of the CNG3B channel is concerned, Applicants contend that, depending on the specific conditions, both activating and inhibitory modulators can be useful for treating problems relating to vision or male fertility. Third, the specification does state specific conditions associated with the claimed CNG3B channels, namely, disorders in vision or male fertility.

In summary, by way of a Rule 132 declaration by Dr. McCormack, Applicants have established that the asserted utility of this invention is specific, substantial, and credible. The specific concerns raised by the Examiner in the Final Office Action are also addressed in this response. Thus, Applicants respectfully request that the utility rejection be withdrawn.

B. 35 U.S.C. §112, First Paragraph: Enablement

Utility-Based Enablement Rejection

Claims 1-9, 18, and 19 were also rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Examiner asserted that since the claimed invention does not

have a patentable utility, one of skill in the art would not know how to use the invention. In light of the above discussion, Applicants trust that sufficient utility under 35 U.S.C. §101 has been established. Thus, the withdrawal of the enablement rejection based on the alleged lack of utility is respectfully requested.

Scope-Based Enablement Rejection

Claims 1, 2, 5, and 7-9 were further rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, as the Examiner argued that the specification does not properly enable the full scope of the claimed invention. Applicants respectfully traverse the rejection.

In their response filed February 1, 2005, Applicants presented arguments that the claimed invention is enabled because the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. Briefly, Applicants pointed out that the claims are directed to a nucleic acid encoding a CNG3B subunit of a cyclic nucleotide-gated cation channel, which has well-defined structures and readily testable functional features. The specification contains ample directions to practice the invention, such as methods for cloning the CNG3B coding sequence, for expressing and purifying a CNG3B polypeptide in host cells, for immuno-detection of the polypeptide, as well as assays for analyzing the electrophysiological characteristics of CNG3B channels and assays for screening compounds that modulate ion flow through CNG3B channels. Applicants also pointed out that, given the high level of technical sophistication in the art, and the fact that variants of CNG3B can be readily made and tested according to the knowledge in the art or the teachings of the specification, that inoperative embodiments can be eliminated.

In the Final Office Action of May 4, 2005, however, the Examiner continued to reject the claims for enablement reasons. The Examiner stated, in the second paragraph on page 9 of the Action, that the claimed invention is not fully enabled because: first, the specification does not describe the portions of CNG3B that are critical for its activity; second, what modifications, such as substitutions, deletions, or additions, can be made to the CNG3B

sequence without loss of functionality; and third, the specification does not provide guidance on how to use that large number of CNG3B variants, which would encompass inactive variants.

The Examiner's concerns are unfounded. First, although the present specification does not contain detailed description of the crucial structural features of CNG3B, a person of skill in the art would readily recognize which portions of the CNG3B polypeptide would be crucial for its functionality. This is because the cation channels of the CNG family are well studied and fully characterized in their structure. For instance, on page 1, lines 28-31, the specification mentions that CNG channel subunits share a common motif of 6 transmembrane domains, a pore motif, and a cytoplasmic cyclic nucleotide binding domain. Furthermore, other beta subunits similar to CNG3B were known in the art at the time this application was filed. *See, e.g.*, Gerstner *et al*, *J. Neurosci.* 20(4):1324-1332, Feb. 15, 2000, for description of another CNG beta subunit, CNGB1. Based on this knowledge, a person of skill in the art would be able to easily perform a sequence comparison and determine the conserved domains among CNG beta subunits. Second, such sequence alignment results would also suggest to an artisan to modify the amino acid residues not conserved among known CNG beta subunits while leaving those conserved residues unchanged, in order to preserve functionality. When the exercise of making CNG3B variants is carried out in such a manner (which is also the only sensible manner in which a person of skill in the art would carry out the task), the possible modifications to the CNG3B sequence are indeed rather limited and definitely not as numerous as the Examiner has asserted. Third, Applicants recognize that the claims may encompass some CNG3B variants that lack the required functionality, but cannot agree with the Examiner's apparent position that in order to meet the enablement requirement, a claim must not encompass any inoperative embodiments. It is well settled that a claim does not fail the enablement test only because it encompasses some inoperative embodiments. "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort that is normally required in the art." MPEP §2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984). In the present case, what an artisan needs to perform to distinguish operative and inoperative

embodiments is a functional assay that is either known in the art or taught in the specification, which is exactly the type of effort "normally required in the art."

The Examiner further cited the references by Wells and Ngo *et al.* to support his contention that the relationship between protein sequence and function is unpredictable. Applicants do not wish to take the position that the conclusions by these authors are erroneous. Applicants do wish to point out, however, that the present case is factually distinct from the situations discussed by Wells and Ngo *et al.* in their papers. As already mentioned above, the CNG cation channels have been the focus of many studies and are in general well characterized structurally. Thus, there exists a closer and far more reliable correlation between the primary amino acid sequence of a CNG channel subunit and its biological function as a CNG cation channel subunit. Segments of the primary amino acid sequence are also assigned to various functional domains (*e.g.*, the pore domain, the transmembrane domains, *etc.*) within the subunit with a high degree of reliability. In direct contrast, the cited references discuss situations in which protein functions are often inaccurately assigned based on the mere presence of a single domain with some level of sequence homology to a known functional domain in other proteins. Due to these clear differences in the fact patterns, the Wells and Ngo references are irrelevant to the present case and cannot provide any support for the enablement rejection.

Lastly, the Examiner cited *Ex parte Maizel*, which indicates that, among other things, one cannot properly claim a DNA sequence by what it does, *e.g.*, encoding a protein exhibiting certain characteristics or a biologically functional equivalent thereof, instead of what it is. Applicants fully agree with the Examiner on this point and submit that the claimed nucleic acid of the present application is indeed defined by what it is, rather than what it does. The claimed nucleic acid is defined by the polypeptide it encodes: aside from its functions, the polypeptide is described as comprising a subsequence having at least 85% (or 90%, or 95%) amino acid sequence identity to SEQ ID NO:1. This is what it is, not what it does.

In summary, Applicants' analysis of the *Wands* factors indicates proper enablement of the claimed invention. The specific concerns raised in the Final Office Action are

also fully addressed. Applicants thus respectfully request the withdrawal of the enablement rejection.

C. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1-9, 18, and 19 were further rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. Applicants respectfully traverse the rejection.

Applicants have previously presented their arguments regarding the written description rejection in their response filed February 1, 2005. Briefly, Applicants pointed out that the claimed genus of nucleic acids is defined by their commonly shared functional features (encoding a polypeptide capable of forming, with at least another alpha subunit, a cyclic nucleotide gated cation channel) and structural features (encoding a polypeptide comprising a subsequence with at least 80% sequence identity to SEQ ID NO:1), and is therefore in full compliance with the written description requirement as set forth by the MPEP and the prevailing case law.

Yet the pending claims remain rejected for alleged inadequate written description. In the Final Office Action of May 4, 2005, the Examiner offered the following reasons for the rejection: first, the claims are drawn to a genus of DNA molecules encompassing a large number of nucleic acids that vary substantially, both in length and in nucleotide composition, whereas the specification describes only two embodiments of the claimed nucleic acids (the first full paragraph on page 12 of the Final Office Action); and second, the specification does not identify any particular structure/function correlation of the claimed nucleic acids, such that a skilled artisan cannot envision the detailed chemical structure of the claimed polypeptides and DNA molecules (the paragraph bridging pages 12-13 and the first full paragraph on page 13 of the Final Office Action). The Examiner further cited *Fiddes v. Baird,* 30 USPQ2d 1481 (Bd. Pat. App. & Int. 1993), to support his conclusion of inadequate written description.

Applicants cannot agree with the Examiner's reasoning. First, written description is assessed based on whether the disclosure reasonably conveys to one of skill in the art that the

inventors, at the time the application was filed, had the claimed invention in their possession. As already discussed above, the CNG cation channels and particularly other CNG channel beta subunits were known in the art. Thus, a person of ordinary skill in the art would reasonably recognize that taking possession of the coding sequence of a new CNG beta subunit CNG3B would mean that the inventors could easily also possess a variety of variants of the CNG3B coding sequence. This is because routine sequence comparison with other CNG beta subunits, the knowledge of functional domains within a CNG cation channel polypeptide, and recombinant DNA technologies would allow an artisan to readily produce such CNG3B variants, whose functionality as a CNG channel beta subunit can then be readily verified in assays known in the art or taught in this application.

Second, the correlation of structural features of a CNG3B polypeptide and its function as a CNG cation channel beta subunit indeed can be gleaned from the specification, given the knowledge in the field of ion channels. CNG cation channel subunits are well studied, their primary amino acid sequences and corresponding secondary or tertiary features, such as the spatial arrangement of their functional domains, to a large extent understood. Given the CNG3B coding sequence and thus the amino acid sequence of the CNG3B polypeptide, an ordinarily skilled artisan would easily recognize which segments of the primary sequence correspond to the functional domains of the CNG beta subunit. In view of the state of the art, it cannot be fairly said that the specification does not provide the correlation between the structural features and the functionality of a CNG3B polypeptide.

In *Fiddes*, the Board ruled that adequate written description was not present to support a broad claim drawn to mammalian fibroblast growth factors (FGF) when only bovine pituitary FGF amino acid sequence and its theoretical nucleotide sequences were disclosed. The Examiner apparently was of the opinion that the facts in *Fiddes* are analogous to that in the present case, such that a finding of inadequate written description in the present application is warranted. Applicants respectfully disagree with the Examiner's reading of the *Fiddes* case and application of *Fiddes* in the present application.

First, *Fiddes* is not inconsistent with the standards for written description as set forth by *Lilly* or *Fiers*. In fact, the Board in *Fiddes* quoted *Fiers* in the discussion of what constitutes adequate written description. 30 USPQ2d at 1483. Moreover, the *Lilly* decision was handed down later in time than *Fiddes* (1997 v. 1993) and by a higher legal authority (Federal Circuit v. the Board). Thus, even if any inconsistency existed, the *Lilly* decision would be controlling over *Fiddes*.

Second, the fact pattern of *Fiddes* is not analogous to that of the present case. In *Fiddes*, a broad claim was drawn to mammalian FGF based on the specification disclosing a bovine FGF amino acid sequence and a ***deduced*** nucleotide sequence, but not any naturally occurring FGF nucleotide sequence. As it later turned out, the deduced nucleotide sequence disclosed in the specification is significantly different from the naturally occurring FGF nucleotide sequence, largely due to codon degeneracy. In essence, the patent applicants in *Fiddes* sought to patent a large genus of polypeptides and polynucleotides when they did not have in their possession any correct polynucleotide sequence. The Board's finding of inadequate written description was based on the notion that the claim of a genus of polynucleotides cannot be adequately supported when only an ***inaccurate*** polynucleotide sequence was disclosed. The Board in *Fiddes* did not take the position that the claim of a genus cannot be adequately supported by the disclosure of an ***accurate*** polynucleotide sequence. Nor could the Board, under *Lilly*, properly require the claim of a genus to be supported by the patent applicant's possession of every embodiment of the genus.

In contrast to *Fiddes*, Applicants of the present application had in their possession both the amino acid sequence of a CNG3B polypeptide (SEQ ID NO:1) and the polynucleotide sequence encoding the polypeptide in full length (SEQ ID NO:2 or 3). In addition, the claims in the present application are not drawn to a broad genus of molecules without specific structural or functional definition (such as simply reciting "mammalian CNG cation channel beta subunits"). As discussed above, both structural and functional features commonly shared by the claimed genus have been described in detail, which reasonably convey to one of skill in the art that Applicants had the claimed invention in their possession.

Taken together, the disclosure by the present application provides both the structural/physical features and functional characteristics of the claimed genus of nucleic acids, fully satisfying the written description requirement under *Lilly* and *Fiers*. On the other hand, there exist crucial factual distinctions between the present case and *Fiddes*, which would make it improper to apply *Fiddes* mechanically. As such, Applicants respectfully request that the Examiner withdraw the written description rejections.

In summary, both structural and functional features commonly shared by the claimed genus of nucleic acids have been described in detail, and the Examiner's specific concerns regarding the written description requirement have also been addressed. Applicants thus respectfully request the withdrawal of the written description rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
60578262 v1